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ORIGINAL REPORT

Phase II Trial of Imatinib in AIDS-Associated Kaposi's Sarcoma: AIDS Malignancy Consortium Protocol 042

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ABSTRACT

Purpose
Kaposi's sarcoma (KS) is a disease of multifocal vascular proliferation that requires infection with KS herpes virus (KSHV/HHV-8). Activation of the c-kit and platelet-derived growth factor (PDGF) receptors by autocrine/paracrine mechanisms follows endothelial cell KSHV infection. In a pilot study, imatinib, a c-kit/PDGF-receptor inhibitor, induced partial regression of AIDS-associated KS (AIDS-KS) in five of 10 patients.

Patients and Methods
This multicenter phase II study was designed to estimate the response rate to imatinib in AIDS-KS. Secondary objectives included investigation of predictors of response and imatinib pharmacokinetics in patients on antiretrovirals. Patients received imatinib 400 mg/day by mouth for up to 12 months with dose escalation up to 600 mg/day at 3 months if their disease was stable.

Results
Thirty patients were treated at 12 AIDS Malignancy Consortium sites. Ten patients (33.3%) achieved partial response, six (20%) had stable disease, and seven (23.3%) exhibited KS progression. Nine patients completed 52 weeks of imatinib therapy. The median treatment duration was 22.5 weeks. Only five patients (16.7%) discontinued therapy owing to adverse events. Antiretroviral regimens did not significantly alter imatinib metabolism. Activating mutations in PDGF-R and c-kit were not found at baseline or at disease progression. We found no correlation with response with changes in any of the candidate cytokines.

Conclusion
Imatinib has activity in AIDS-KS. Pharmacokinetic interactions with antiretroviral drugs did not correlate with toxicity. Thirty percent of patients showed long-term clinical benefit and remained on imatinib for the entire year. These results suggest imatinib is well tolerated and may be an alternative therapy for some patients with AIDS-KS.

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INTRODUCTION

Kaposi's Sarcoma (KS) is a disease of multifocal vascular proliferation, predominantly involving the skin but also visceral organs. AIDS-associated KS (AIDS-KS) requires host coinfection with HIV and the Kaposi's sarcoma herpes virus (KSHV, also known as human herpesvirus–8).[1] KSHV drives tumor formation by inducing cytokines such as vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), stem-cell factor, and platelet-derived growth factor (PDGF), which act by autocrine and paracrine mechanisms.[2-8]

The PDGF and c-kit receptors play critical roles in KS development. KSHV infection of endothelial cells results in a five-fold upregulation of the c-kit receptor and KSHV-infected endothelial cell cultures proliferate in response to the c-kit ligand, stem-cell factor.[8] PDGF induces expression of VEGF by cultured KS spindle cells.[7] The βPDGF-receptor (PDGF-R) is expressed in KS tumor specimens, and adding PDGF to cultured KS spindle cells induces expression of VEGF.[7] This potential role of PDGF-R and c-kit in KS cell proliferation and induction of angiogenesis through VEGF makes inhibition of these receptors an attractive therapeutic target.

Imatinib is a tyrosine kinase inhibitor initially approved by the US Food and Drug Administration for treatment of chronic myeloid leukemia.[9] In preclinical studies, imatinib was found to be a potent inhibitor of BCR-ABL, PDGF-R, and the c-kit

receptor. Imatinib has also shown activity against gastrointestinal stromal tumors, which are dependent on c-kit, and against dermatofibrosarcoma protuberans and hypereosinophilic syndrome, which depend on activation of the PDGF pathway.[10,11] Consequently, we sought to test the clinical utility of PDGF and c-kit receptor inhibition in AIDS-KS.

In a pilot trial of 600 mg of imatinib therapy administered once daily in AIDS-KS, five of 10 patients achieved at least a partial response (PR) after only 4 weeks of imatinib therapy.[12] Six of 10 patients required dose reduction to 400 mg daily because of gastrointestinal toxicity.[12] Thus, the dose regimen of 400 mg once daily was chosen for our current trial. Response and progression correlated with bFGF, interferon gamma (IFNγ), and Rantes (CCL5) baseline concentrations.[12] The AIDS Malignancy Consortium (AMC) therefore initiated AMC 042, a phase II multicenter trial, to determine the response rate of imatinib on AIDS-KS, investigate potential pharmacokinetic (PK) interactions between imatinib and antiretroviral therapies, and explore mechanisms of response.

PATIENTS AND METHODS

Patients

Twenty-nine men and one woman with biopsy-proven AIDS-KS were enrolled at 12 AMC sites (Fig 1). Two thirds of the patients were members of racial or ethnic minorities. All patients provided written, informed consent. The protocol and consent were approved by each site's institutional review board in accordance with human experimentation guidelines of the Human Investigations Committee at the member institutions. Patients were required to have measurable KS involving the skin. Additional eligibility criteria included documentation of HIV infection by enzyme-linked immunosorbent assay (ELISA) or Western Blot, a Karnofsky performance status $\geq$ 60%, and the following laboratory parameters: hemoglobin $\geq$ 8.0 gm/dL, absolute neutrophil count $\geq$ 1,000 cells/μL, platelet count $\geq$ 75,000/μL, serum creatinine $\leq$ 1.5 mg/dL (or measured creatinine clearance $>$ 60 mL/min), AST/ALT less than three times the upper limit of normal, and a normal total serum bilirubin. Exclusion criteria included concurrent active opportunistic infection and symptomatic visceral KS requiring cytotoxic therapy. Patients could not have received any treatment for KS within 4 weeks of study entry. Antiretroviral therapy was permitted but not required. Patients taking antiretroviral therapy could not have had a medication change within 4 weeks of study entry. No blood products were permitted within 4 weeks of study entry. Granulocyte colony-stimulating factor (G-CSF) and erythropoietin were not permitted within 2 weeks of study entry.

Study Design

Patients received imatinib 400 mg orally once daily for 4-week cycles. Patients continued on study for up to six cycles as long as their KS did not progress. If after at least three cycles patients had stable disease and exhibited no therapy-related toxicities, patients' doses could be increased to 600 mg/day. Patients achieving objective response or stable disease after six cycles could continue on study for an additional seven cycles (for 52 weeks total). Treatment was discontinued for tumor progression, unacceptable toxicity that was unresponsive to dose modifications, or completion of the 52-week study period. Clinical assessments and laboratory studies occurred during cycle 1 on days 1, 8, and 15, and then on day 1 of every cycle thereafter. Formal tumor assessment was performed at baseline, day 1 of cycles 2 and 3, and then every second cycle thereafter. CD4+ counts and HIV-plasma RNA levels were measured at baseline, on day 1 of cycle 2, and every three cycles thereafter. Plasma for cytokine sampling was drawn at baseline and day 29. Tumor punch biopsies were performed at baseline and day 8 to assess for inhibition of PDGF/c-kit signaling, as well as at baseline and at the time of progression to assess for activating and resistance mutations in the βPDGF and c-kit receptors.

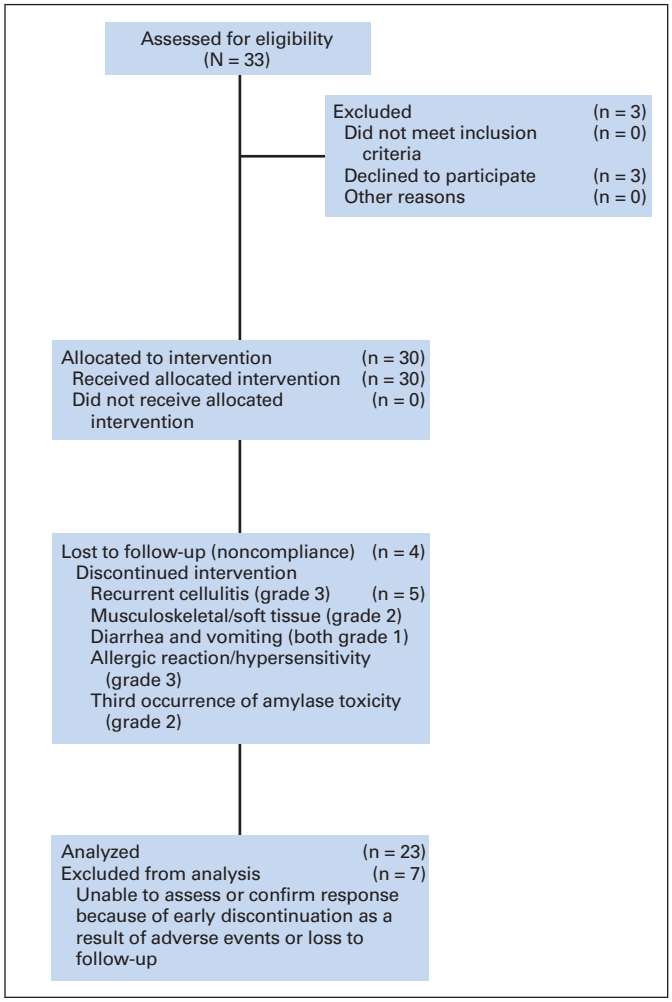

Fig 1. AIDS Malignancy Consortium 042 trial (AMC042) flow diagram.

Dose reductions were permitted to reduce toxicity. No dose reductions occurred for grade 2 hematologic toxicities. For grade 2 nonhematologic toxicities, the study drug was withheld until the toxicity resolved to grade 1 or lower. Imatinib was then resumed at the same daily dose. If the grade 2 toxicity recurred, imatinib was again withheld until the toxicity decreased to $\leq$ grade 1, and the daily dose was then reduced by 100 mg if at the 400-mg dose level, or by 200 mg if at the 600-mg dose level. For all grade 3 and 4 level toxicities (with the exception of hypophosphatemia), imatinib was withheld until the toxicity level decreased to $\leq$ grade 1 or baseline for nonhematologic toxicities or decreased to grade 2 for hematologic toxicities. The daily dose was then reduced by 100 mg if at the 400-mg dose or by 200 mg if at the 600-mg dose. If grade 3 or 4 level toxicities recurred, imatinib was stopped. Patients could receive G-CSF as clinically indicated. No dose reductions were performed for any grade anemia; patients could receive transfusions or erythropoietin at the discretion of the investigator.

After the protocol was opened, we recognized hypophosphatemia and low vitamin D levels may develop in patients taking imatinib.[13] Imatinib may interfere with osteoclast function directly by inhibiting βPDGF-R on osteoclasts or indirectly by inhibiting activation of C-FMS receptor. The protocol was modified to include phosphate screening, and a vitamin D and phosphate repletion schema was incorporated into the protocol.

Pharmacokinetic Studies

Imatinib PK was assessed in the first 12 patients after a single or multiple doses on days 1 and 15. Serial sampling of venous blood was performed before treatment and at 0.5, 1, 2, 3, 4, 8, and 24 hours after treatment. Samples were

Table 1. Sequencing Primers

Primers		Forward Primers	Reverse Primers
βPDGF-R	Exon 12	5′-GCTGTGTGACTTCAAATATGCCCCTG-3′	5′-ATCATAGAACCTCAATGCTAGGCAGTTCC-3′
	Exon 18	5′-GCACATGGGCAGTGTTGTATTTTCC-3′	5′-ATCACGTTTTAACCAGACCAATCCCTGCTAC-3′
CKIT	Exon 11	5′-GTACAATGTAACCAAGGTGAAGCTCTGAGAC-3′	5′-ATTTCACAGAAAACTCATTGTTTCAGGTGG-3′
	Exon 17	5′-TGTGAACATCATTCAAGGCGTACTTTTG-3′	5′-TTAATATTTTTCACACGGCATGCCAATC-3′

collected in heparinized tubes and were centrifuged at 2,400 × *g* for 5 minutes. Plasma was frozen at −80°C until the time of analysis. Plasma concentrations of imatinib and its main metabolite (CGP-74588) were determined using a validated liquid chromatographic-mass spectrometric assay over the concentration range of 0.03 to 10 μg/mL.[14] PK variables were calculated by standard noncompartmental methods using WINNonlin professional (version 5.3; Scientific Consultant, Apex, NC) as previously described.[15]

KS Biopsy Mutation Analysis and Immunohistochemistry

KS biopsies for mutation analysis were placed in RNAlater (Qiagen, Alameda, CA) storage media. DNA was extracted using trizol. Genomic DNA was amplified using primers for exons 12 and 18 in βPDGF-R, and exons 11 and 17 in KIT. The primers are listed in Table 1. These amplified products were analyzed using Mutation Surveyor (SoftGenetics, State College, PA) software to detect the presence of activating mutations or mutations that could confer resistance to imatinib.

KS biopsies for PDGF/c-kit signaling analyses were immediately placed in formalin for fixation. After paraffin embedding, 1-mm cores were taken from an area containing lesional cells and were placed in a tissue microarray. Tissue sections 5-mm thick were prepared from the tissue microarray and were stained using antiphospho-ERK (Threonine 202/Tyrosine 204) antibody (Cell Signaling, Beverly, MA). Slides were deparaffinized in xylene and ethanol. Antigen retrieval was performed by boiling the slides for 10 minutes in pH6 citrate buffer. The slides were cooled for 30 minutes. After 10 minutes in 3% H_2O_2, slides were incubated overnight with the primary antibody at 1/100 dilution at 4°C. This was followed by 30 minutes' incubation with 100 mL of biotinylated antirabbit secondary antibody, and then another 30 minutes with ABC avidin/biotin (Vector Labs, Burlingame, CA). Slides were incubated in ethanol and xylene before mounting coverslips. Staining was then scored on a scale of 0 to 3+ by a blinded dermatopathologist (K.H.).

Cytokine Concentrations

Serum and plasma specimens for cytokine profiles were collected at baseline and on day 29. Concentrations of IFNγ, Rantes, interleukin-6 (IL-6), and bFGF were measured using the Mesoscale platform.[16]

Statistics and Response Criteria

The study used Simon's two-stage design[17] to test the null hypothesis that the overall response (complete response plus PR) rate was ≤ 20%, against the alternative hypothesis that it was at least 50% at the one-sided 0.10 significance level with power of 0.90. The overall response rate was estimated using the binomial proportion and its exact one-sided 95% CI. The null hypothesis was tested using the *z* test. We chose 20% as the threshold for the null hypothesis based on the randomized, double-blinded, placebo-controlled phase III study IM862, in which patients on the placebo arm showed a response rate of 21%.[18] Ten patients were to be enrolled in the first stage. The study was to be stopped if no more than two patients responded and was to be continued if at least three patients responded to the therapy, for a total of 22 evaluable patients. After 10 patients were enrolled, three responses were observed. With a 20% to 25% dropout rate, 30 patients were enrolled to ensure 22 evaluable patients.

PK parameters were summarized by descriptive statistics based on whether the antiretroviral regimen contained efavirenz, ritonavir, or neither efavirenz nor ritonavir. PK parameters were compared using either Kruskal-Wallis analysis of variance or Wilcoxon signed-rank tests. All *P* values were two-sided, were not adjusted for multiple comparisons, and were considered significant at a $P < .05$. We assessed response to treatment in accordance with previously described criteria.[19]

RESULTS

Patient Characteristics

Thirty patients were treated on the study at 12 AMC sites from August 2005 until April 2007 (Table 2). Patients' median age was 43 years, and the median CD4 count was 263/μL. Most patients had previously received antiretroviral therapy, and approximately three-fourths of the patients had HIV viral load levels below assay detection level. Sixty percent of patients had previously received therapy for KS. Fifty-seven percent of patients received prior chemotherapy.

Clinical Events

The median treatment duration was 22.5 weeks (range, 0.3 to 52.7 weeks; Table 3). Nine patients (30%) completed the entire 52-week treatment (13 cycles) per protocol. Seven patients (23%) terminated treatment because of disease progression, and five patients

Table 2. Demographic Summary and Selected Baseline Characteristics

Characteristic	No. of Patients	%
Sex		
Male	29	96.7
Female	1	3.3
Age, years		
No. of patients	30	
Median	42.8	
Min-max	27.9-68.8	
Absolute CD4+ cell count at baseline		
No. of patients	30	
Median	263	
Min-max	19-819	
Prior antiretroviral therapy		
No	7	23.3
Yes	23	76.7
HIV viral RNA level, copies/mL*		
No. of patients	28	
Geometric mean	217.3	
95% CI	72.7 to 649.6	
Median	50	
Min-max	2-595,660	
Below limit of detection*	22	78.6
Prior treatment for KS		
1: Yes	18	60.0
2: No	12	40.0

Abbreviations: KS, Kaposi's sarcoma; max, maximum; min, minimum.
*For two patients, baseline HIV viral levels were not collected.

Table 3. Clinical Effect

Effect	No. of Patients	%
Best response		
Partial response	10	33.3
Stable disease	6	20.0
Progressive disease	7	23.3
Unevaluable*	7	23.3
Time to response, weeks	10	
Median	21.0	
Min-max	3.0-40.1	
Response duration, weeks	10	
Censored	7	70
Median	36	
95% CI for median	14.0–not reached	

Abbreviations: AE, adverse event; max, maximum; min, minimum.
*Three patients withdrew because of AEs (nausea and vomiting, n = 2; hives/angioedema, n = 1). Four patients were discontinued from study because of their inability to keep up with scheduled visits.

(17%) terminated treatment because of adverse events. Ten (33.3%) of 30 patients achieved a partial response and six (20%) of 30 patents had stable disease. There were no complete responses. Thus, the overall response rate is 33.3% (one-sided 90% CI, 21.8% to 100%) and is significantly higher than 20% ($P = .034$). The median time to response was 21 weeks; the median response duration was 36 weeks. The median time to progression for patients with PR or stable disease was 48 weeks. Most patients (70%) reported adverse events (all grades) but only 11 grade 3 or 4 (severe or life-threatening) adverse events were reported, of which eight were attributed to the study drug (Table 4). No grade 3/4 neutropenia requiring G-CSF occurred. No significant changes in HIV viral load or CD4+ cell counts were observed. There was no correlation with CD4+ cell count and tumor response, however, the median HIV viral load was significantly lower ($P = .05$) in patients who had a PR or stable disease (median viral load, 50 copies/mL) compared with patients whose disease progressed (median viral load, −400 copies/mL).

Imatinib Pharmacokinetics

Consistent with previous reports, imatinib and the metabolite exhibited large intrapatient variability (Table 5).[15] There was a trend for patients receiving efavirenz to have lower exposure (area under the curve) than patients on a nonefavirenz/nonritonavir regimen, but this did not reach statistical significance ($P > .05$). For ritonavir, a trend was noted toward higher metabolite exposure (area under the curve) on day 1, which did not reach statistical significance ($P > .05$).

Table 4. Grade 3/4 Adverse Events Attributed As Possibly, Probably, or Definitely Related to Study Drug

		No. of Patients	
Category	Adverse Event	Grade 3	Grade 4
Allergy/immunology	Allergic reaction/hypersensitivity (including drug fever)	1	
Gastrointestinal	Dehydration	1	
	Nausea	1	
Infection	Infection with normal ANC or grade 1 or 2 neutrophils/skin (cellulitis)	1	
Metabolic/laboratory	Creatine phosphokinase		1
	Phosphate, serum-low (hypophosphatemia)	2	
Neurology	Mood alteration/depression	1	

Abbreviation: ANC, absolute neutrophil count.

Activation of the PDGF-R and c-kit Pathways

We hypothesized that KS may be driven by mutations in the βPDGF or c-kit receptors and that mutations in these receptors may contribute to imatinib resistance. We sequenced the juxtamembrane and kinase domain in both receptors, as these are where the majority of activating mutations of c-kit and αPDGF receptors have been reported. We used mutation surveyor software to probe exons 12 and 18 in βPDGF-R, and exons 11 and 17 in c-kit for mutations. We found no mutations in any patients at baseline or in the 12 patients for whom we collected biopsies at the time of tumor progression.

Inhibition of PDGF-R and c-kit Targets

In our pilot study, we investigated whether imatinib inhibited downstream effectors of c-kit and PDGF-R. Imatinib had shown decreased phosphorylation of ERK but no effect on AKT phosphorylation at day 30, suggesting that target receptors were inhibited.[12] In this study, we investigated whether ERK was phosphorylated at day 8, a timepoint at which we estimated that steady-state concentrations of imatinib would be achieved. We observed no significant decrease in ERK phosphorylation in the day-8 biopsies when compared with baseline.

Plasma Cytokine Concentrations

In our pilot study, response to imatinib correlated with baseline concentrations of IFNγ and Rantes or changes in IL-6 and bFGF at day 28. In the current study, plasma concentrations of IFNγ, Rantes, IL-6, and bFGF were measured using the Mesoscale platform. We found no correlation with response with baseline levels or changes in any of the candidate cytokines (data not shown).

DISCUSSION

Our study demonstrates imatinib therapy has significant activity (PR, 30%; stable disease, 20%) against AIDS-KS. We also investigated inhibition of target pathways, mechanisms of toxicity, and biomarkers of response. In our earlier pilot study, we found inhibition of ERK in day-30 biopsies when compared with baseline biopsies.[12] In the current study, we observed a trend toward inhibition of ERK in the biopsies at day 8 but it did not reach statistical significance. We chose day 8 as the time-point to investigate ERK phosphorylation because we predicted the imatinib levels would be at steady-state based on the terminal half-life for imatinib reported in other settings.[20] Our PK analysis confirmed our initial assumptions as no patient had a terminal half-life of more than 33 hours on day 15. We observed no correlation between ERK inhibition and levels of imatinib or its metabolite (data not shown). Given that we achieved adequate drug levels based on the experience in other imatinib-responsive tumors, this discordance may have a number of explanations. ERK activation may be mediated through other pathways and, by choosing an earlier timepoint for studying ERK activation, we may not have observed the decrease in ERK phosphorylation observed at day 30 in the pilot study.

Table 5. Plasma Pharmacokinetic Parameters of Imatinib and CGP-74588)

Antiretroviral Regimen and Day Administered	Imatinib			CGP-74588			CGP-74588:Imatinib Ratio (%)		
	Efavirenz (n = 4)	Ritonavir (n = 5)	Non-Efavirenz/ Non-Ritonavir (n = 3)	Efavirenz (n = 4)	Ritonavir (n = 5)	Non-Efavirenz/ Non-Ritonavir (n = 3)	Efavirenz (n = 4)	Ritonavir (n = 5)	Non-Efavirenz/ Non-Ritonavir (n = 3)
AUC (μg*h/mL)									
1	29.6 ± 14.1	41.6 ± 33.3*	44.4 ± 18.9	4.7 ± 2.4	9.9 ± 3.9*	6.6 ± 1.2	16.8 ± 5.0	29.6 ± 10.5*	16.2 ± 4.9
15	38.8 ± 14.0	40.8 ± 29.8*	45.1 ± 7.5	5.5 ± 1.2	11.8 ± 13.1*	12.1 ± 0.5	14.8 ± 2.6	25.4 ± 10.9*	27.1 ± 3.6
C_{max} (μg/mL)									
1	2.2 ± 0.3	2.4 ± 1.1	1.9 ± 0.5	0.27 ± 0.03	0.27 ± 0.06	0.24 ± 0.09	NR	NR	NR
15	2.8 ± 0.7	3.0 ± 1.8	2.8 ± 0.5	0.34 ± 0.08	0.69 ± 0.78	0.69 ± 0.08	NR	NR	NR
T_{max} (h)									
1							NR	NR	NR
Median	2.0	3.0	2.0	2.0	3.0	2.0			
Range	2.0-4.0	2.0-3.0	1.0-4.0	0.5-3.0	2.0-4.0	2.0-4.0			
15							NR	NR	NR
Median	3.0	2.0	1.0	2.0	2.0	2.0			
Range	2.0-4.0	1.0-4.0	1.0-4.0	1.0-4.0	1.0-4.0	1.0-4.0			
$T_{1/2}$ (h)									
1	10.0 ± 3.7	11.3 ± 4.0*	18.1 ± 10.7	14.1 ± 3.6	27.1 ± 7.6*	23.2 ± 7.3	NR	NR	NR
15	12.2 ± 2.1	12.6 ± 6.8†	21.9 ± 11.6	30.5 ± 9.1*	36.5 ± 11.8†	39.5 ± 23.2	NR	NR	NR
Cl/F (L/h)									
1	16.4 ± 8.7	14.8 ± 10.4*	10.0 ± 3.6	NR	NR	NR	NR	NR	NR
15	11.4 ± 4.2	13.4 ± 7.1*	9.0 ± 1.5	NR	NR	NR	NR	NR	NR

NOTE. Data are presented as mean ± SD. T_{max} is presented as median and range. If $n < 3$, the actual values are reported.

Abbreviations: AUC∞, area under the plasma concentration-time curve to infinity for day 1 data; AUC_{τ}, AUC for the dosing interval for day 15; C_{max}, peak plasma concentration; Cl/F, apparent clearance; NR, not reported; SD, standard deviation; $T_{1/2}$, half-life; T_{max}, time to peak concentration.

*One patient fewer than total No. of patients, owing to incomplete sampling collection.

†Two patients fewer than No. of patients owing to incomplete sampling collection on one patient and a poor correlation for $T_{1/2}$ on another.

Also, while we were conducting this trial, a number of studies recognized that small variations in specimen handling might result in variability when assessing phospho-epitopes as markers of drug efficacy.[21,22] Unfortunately, the antibody we used to assess βPDGF-R phosphorylation by immunohistochemistry in our pilot study was later found to cross-react with other membrane-bound receptors and is no longer recommended for immunohistochemistry use. The lack of correlation with drug levels and immunohistochemical changes highlights the difficulty of using phospho-epitopes as biologic end points within the setting of multicenter trials.

Though trends suggesting alterations of imatinib metabolism were observed between the patients receiving efavirenz-, ritonavir-, or nonefavirenz/nonritonavir-containing regimens, there was no statistically significant difference. This may be due in part to the small sample size, given the large intrapatient variability typically noted with imatinib. In gastrointestinal stromal tumors, c-kit, and PDGF-R–driven tumors, plasma imatinib levels of 1,000 ng/mL have been associated with response. We did not observe any correlation between day 15 imatinib levels and response; however, only eight of the 12 patients with PK data were evaluable for response. Although we cannot confirm we achieved target inhibition because of the technical limitations of the assays, our data suggest that the mechanism of resistance to imatinib is not a consequence of inadequate drug levels owing to shortened terminal half-life.

Although we observed tumor regression with imatinib therapy, we did not detect activating mutations in the c-kit or βPDGF-R receptors. We may have failed to detect these mutations if they occurred in only a small fraction of the KS cells. However, even if they occur in only a small population of tumor cells, our results support the concept that c-kit and βPDGF-R are activated through autocrine or paracrine mechanisms. In addition, the absence of mutations in the patients whose KS progressed while they were receiving imatinib treatment or whose tumors did not respond to treatment suggest that other mechanisms mediate imatinib resistance in this setting. In our pilot study, response to imatinib correlated with baseline concentrations of IFNγ and Rantes and changes in IL-6 and βFGF concentrations at 28 days. In this larger study, we observed no correlation with response and cytokine levels. These data suggest that sequencing c-kit and βPDFG-R or monitoring cytokine levels are not useful in predicting imatinib response of AIDS-KS patients.

Although one fifth of the patients discontinued the treatment because of adverse events, almost one third of the patients stayed on the regimen and showed clinical benefit for the entire 52-week study period. In the pilot study, the longest duration of response was 26 weeks. Based on this observation, we set the maximum treatment period for this study at 52 weeks. We are aware, however, that some patients continued on the commercial drug after study completion, but the study design did not allow for continued follow-up.

Our PK studies are suggestive of an interaction with antiretroviral drugs but, with close monitoring, toxicities were manageable. This regimen may be useful as an alternative for patients who do not require cytotoxic chemotherapy or whose disease has progressed on conventional therapy. Exploration in classic KS may also be warranted, particularly, because this is a disease of the elderly who may benefit from noncytotoxic therapies. Further studies of pathogenesis-based treatments that minimize toxicities are need in this viral and cytokine-driven disease.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) and/or an author's immediate family member(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.
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Appendix

Kaposi's sarcoma response criteria: Definition of response. Complete response is defined as the absence of any detectable residual disease, including tumor-associated edema, persisting for at least 4 weeks. In patients in whom pigmented (brown or tan) macular skin lesions persist after apparent complete response, biopsy of at least one representative lesion is required to document the absence of malignant cells. In patients known to have had visceral disease, an assessment at restaging with appropriate endoscopic or radiographic procedures should be made.

Clinical complete response is defined as the absence of any detectable residual disease, including tumor-associated edema, persisting for at least 4 weeks; *and* for patients with pigmented (brown or tan) macular skin lesions persisting after apparent complete response, biopsy of a representative lesion documenting the absence of KS cells is not required; *and* for patients known to have had visceral disease, restaging with appropriate endoscopic or radiographic procedures is contraindicated or otherwise not performed.

Partial response is defined as no new lesions (skin or oral), or no new visceral sites of involvement (or the appearance or worsening of tumor-associated edema or effusions); *and* a 50% or greater decrease in the number of all previously existing lesions lasting for at least 4 weeks; *or* complete flattening of at least 50% of all previously raised lesions (ie, 50% of all previously nodular or plaque-like lesion become macules); *or* a 50% decrease in the sum of the products of the largest perpendicular diameters of the marker lesions.

NOTE. Patients with residual tumor-associated edema or effusion who otherwise meet the criteria for complete response will be classified as having a partial response.

Stable disease is defined as any response not meeting the criteria for complete response, partial response, or progressive disease.

Progressive disease is defined as follows. For patients with fewer than 50 cutaneous lesions, a 25% increase in the sum of perpendicular diameters of the indicator lesions; *or* a 25% increase in the total lesion count, or a minimum of 5 new lesions, whichever is greater; *or* a 25% increase in the number of raised lesions (minimum of five new raised lesions if there are few raised lesions, for example $\leq$ eight), whichever is greater.

NOTE. There are body sites in which disease is particularly difficult to evaluate, and a few new lesions may be counted despite the fact that a patient is not actually progressing. For example, lesions of the foot, particularly those which are flat, are difficult to evaluate because their intensity may be variable based on how much edema is present, how much the person walked the day before, how long their feet have been in a dependent position before the physical exam, and so on.

For patients with more than 50 cutaneous lesions: a 25% increase in the sum of the perpendicular diameters of the indicator lesions; *or* a 25% increase in the total number of lesions in the prospectively defined anatomic sites containing representative numbers of lesions; *or* a total of five new lesions in anatomic sites that were previously documented as having no evidence of cutaneous disease on the whole body diagram; *or* a 25% increase in the number of raised lesions. Photographic documentation of gross or significant progression, particularly in areas that did not receive follow-up, will be of particular value.

NOTE. In order to classify a response as partial response (PR), the patient must have at least a PR in either the cutaneous or noncutaneous sites of the disease and no evidence of progression as defined in the above criteria. In order to classify a response as a complete response (CR), the patient must have a CR in both the cutaneous (if applicable) and noncutaneous (if applicable) sites of disease and no evidence of progression as defined by the above criteria.

Noncutaneous progression. Progressive disease includes new visceral sites of involvement or progression of visceral disease or the development of new or increasing tumor-associated edema or effusion lasting at least 1 week, which interferes with the patient's normal activities. Progressive visceral disease, for measurable and evaluable disease, should be based on RECIST criteria.